

REMARKS

I. Status of the Application

Claims 1-3, 6, 12, 14, 15, 52-54, 56-60, 70-71, and 73-76 are presently pending in the application contrary to the Examiner's indication in the present Office Action that claims 1-3, 6, 12, 14, 15, 52-60, and 70-76 are pending in the present application. Applicants respectfully direct the Examiner's attention to the "Response to Election of Species" dated February 11, 2002 where Applicants elected claims 1-3, 6, 12, 14, 15, 52-54, 56-60, 70-71, and 73-76, thereby withdrawing claims 55 and 72. Accordingly, prior to the present paper, claims 55 and 72 stood withdrawn.

Applicants thank the Examiner for withdrawing the previous objections to the specification and claims denoted "A-O", which were cited in the Office Action dated October 28, 2002. Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 stand rejected under 35 U.S.C. § 112, ¶2. Claims 1-2, 6, 12, 15, 52, 53, 55, 56, 57, 70-73 stand rejected under 35 U.S.C. § 102(b) over US 5,242,974 to Holmes ("the '974 patent") and US 5,679,773 to Holmes ("the 773 patent"). Claims 1-2, 6, 12, 15, 52, 53, 55, 57, 60, 70-72, and 76 stand rejected under 35 U.S.C. § 102(b) over MacDonald et al., *Acc. Chem. Res.*, 27(6):151 (1994) ("MacDonald").

Further, the Examiner is presently applying the following new rejections. Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 stand rejected under 35 U.S.C. § 112, ¶1 regarding new matter. Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 stand rejected under 35 U.S.C. § 112, ¶1 pursuant to the written description requirement. Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 stand rejected under 35 U.S.C. § 112, ¶2. Applicants respectfully traverse all of the foregoing rejections.

Applicants have amended claims 59 and 75 to correct an inadvertent error of a typographical nature. Specifically, claims 59 and 75 now define 1,1-bis[p-chlorophenyl]-2,2,2-

trichloroethane instead of 1,1-bis[*p*-chlorophenyl]-2,2,2-trichloroethane. Applicants submit that such error was made in good faith and that entry of the amendment to claims 59 and 75 will not present new matter.

II. Claims 5, 11, 55, 61-69, 72, and 77-83 Previously Withdrawn Are Now Cancelled

The Examiner indicates at page 2, paragraph 4 of the present Office Action that a complete reply to the present final rejection must include cancellation of presently pending non-elected withdrawn claims (i.e., claims 5, 11, 61-69, and 77-83) or other appropriate action. Accordingly, Applicants are canceling claims 5, 11, 61-69, and 77-83 (and similarly non-elected withdrawn claims 55 and 72) without prejudice to Applicants' right to prosecute such claims in this or any other patent application, including, without limitation, any future continuation, division, continuation-in-part, reissue, reexamination or other application.

III. Claims 1-3, 6, 12, 14, 15, 52-54, 56-60, 70-71, and 73-76 Are Definite

Claims 1-3, 6, 12, 14, 15, 52-60, and 70-76 stand rejected under 35 U.S.C. § 112, ¶2. Applicants respectfully traverse this rejection in view of the following remarks.

Specifically, the Examiner asserts that the term "masked acid" in claims 3 and 54 is not defined by the claim or the specification and is indefinite and/or unclear. Applicants respectfully disagree because the phrase "masked acid" is described in the specification, for example, at page 20, line 28 – page 21, line 1:

In some preferred embodiments of polynucleotide synthesis, **masked acids** including esters, anhydrides, and nitrites are **used as autocatalyst**. In one preferred specific embodiment, the RAC [*ed: Radiation Activated Catalyst*] is a PAAC [*ed: Photo-Activated Acid Catalyst*] which generates an acid upon exposure to radiation of suitable wavelength. The catalytic enhancer is an ester labile to acid-catalyzed thermolytic cleavage by the acid produced by the PAAC.

The enhancer, itself, produces an acid which is used to removed [*sic: remove*] an acid labile protective group. (Emphasis added).

The term “masked acid” denotes a type of an autocatalyst, as indicated immediately above. At page 4, line 5, Applicants explain that an autocatalyst is also known as an “enhancer” (or catalytic enhancer). As indicated in the above-cited portion of the disclosure, the enhancer is an ester labile to acid-catalyzed thermolytic cleavage by the acid produced by the PAAC. The above-cited portion of the application further explains that the masked acid produces an acid capable of removing an acid-labile protective group. Further, Applicants disclose at page 21, lines 3-4 an exemplary preferred catalytic masked acid for polynucleotide synthesis, i.e., 1,4-cyclohex-2-enediylbis(pentafluorobenzoate). Thus, Applicants believe that a person of ordinary skill in the art given the benefit of the disclosure would be able to determine *a priori* all possible compounds that would fall within the category of “masked acids.” Specifically, masked acids comprise all acids, esters, anhydrides or nitrites capable of removing an acid-labile protecting group. Accordingly, because the scope of the term “masked acid” would be clear to a person of ordinary skill in the art, Applicants respectfully request withdrawal of the present rejection.

In addition, the Examiner asserts that the phrase “forming a surface” is not defined by the claim or the specification and is indefinite and/or unclear. Applicants have amended claims 1, 52, and 70 to make the metes and bounds of such claims and their respective dependent claims clearer. That is, claims 1, 52, and 70 now define, in part, applying to a surface a catalyst system. Support for the amendment to each claim can be found throughout the specification, for example, at page 3, lines 27-28: “The photo activated catalyst by itself or in combination with additional catalytic components is referred to herein as a catalyst system.” Accordingly, Applicants respectfully request withdrawal of the present rejection.

IV. Claims 1-2, 6, 12, 15, 52, 53, 55, 56, 57, 70-73 Are Patentable over Holmes ('974) and Holmes ('773)

Claims 1-2, 6, 12, 15, 52, 53, 55, 56, 57, 70-73 stand rejected under 35 U.S.C. § 102(b) under US 5,242,974 to Holmes ("the '974 patent") and US 5,679,773 to Holmes ("the '773 patent"). Applicants respectfully traverse this rejection.

Independent claims 1 and 52 are patentable over the '974 patent at least because the '974 patent fails to disclose a catalyst system comprising a radiation sensitive compound or group defined by claim 1 (or a photosensitive compound or group defined by claim 52), the radiation sensitive compound or group (or the photosensitive compound or group) producing a catalyst when irradiated, and an autocatalytic compound or group, the autocatalytic compound or group generating a protecting group removing product when the autocatalytic compound is activated by the catalyst. In addition, with regard to independent claim 70, the '974 patent fails to disclose at least applying to a surface a catalyst system comprising a synthesis intermediate having an acid removable protecting group, and a photosensitive acid, compound, or group, the photosensitive acid, compound, or group producing an acid when irradiated. Instead, the '974 patent teaches a method for cyclization and reversal of the polarity of polymers on a substrate. The Examiner appears to admit these deficiencies of the '974 patent by citing the '773 patent to show the alleged inherent properties of the NVOC group.

Accordingly, the Examiner asserts at page 6 of the present Office Action that the NVOC protecting group disclosed in the '773 patent reads on parts (i) and (ii) of claim 1. Specifically, the Examiner asserts that the '773 patent discloses the NVOC protecting group functioning as a radiation (light) sensitive compound, a catalyst (6,6-bisveratric acid catalyzes the formation of more 6,6-bisveratric acid), and an autocatalytic compound (6,6-bisveratric acid catalyzes the removal of the NVOC protecting group). Applicants respectfully traverse the Examiner's

assertion because the '773 patent does not show that the NVOC protecting group is necessarily functioning: (1) as a catalyst and/or; (2) an autocatalytic compound.

First, it is apparent from column 18, lines 43-54 of the '773 patent that the NVOC protecting group (or 6,6-bisveratric acid for that matter) is not functioning as a catalyst:

Photodeprotection of the growing oligomer is typically conducted in an **organic solvent containing an acid such as sulfuric acid**. When the protecting group is an NVOC group, photodeprotection leads to the production of 6-nitrosoveratraldehyde as an unstable intermediate which, upon **acid catalysis**, forms 5,6-dimethoxy-2,1-benzisoxazol-3(1H)-one. Further photolysis of the latter species produces 6,6-azo-bisveratric acid. Azo species are typically formed from nitrene intermediates which have the potential to produce a number of undesirable side reactions. As a result, the present invention provides a number of methods for reducing the amount of the nitrene which is formed. (Emphasis added).

From the above-cited portion of the '773 patent, it is apparent that *sulfuric acid* catalyzes the conversion of 6-nitrosoveratraldehyde to 5,6-dimethoxy-2,1-benzisoxazol-3(1H)-one – not the NVOC group or 6,6-bisveratric acid, as the Examiner suggests. Certainly, the '773 patent does not disclose how the NVOC group affects the rate of any reaction.

Second, it is apparent from column 18, lines 43-54 of the '773 patent (quoted above) that contrary to the Examiner's assertion, the NVOC protecting group is not functioning as an autocatalytic compound, and 6,6-bisveratric acid is not catalyzing the removal of the NVOC protecting group. Applicants explain at page 3, lines 15-18 that an autocatalytic compound "chemically alters the synthesis intermediate in a manner to allow the synthesis intermediate to chemically combine with a later added synthesis intermediate or other compound." It is apparent from column 18, lines 43-54 of the '773 patent that the NVOC protecting group is not altering the synthesis in a manner to allow a synthesis intermediate to chemically combine with a later added synthesis intermediate or other compound. That is, 6,6-bisveratric acid is not catalyzing the removal of the NVOC

protecting group. In fact, it is apparent from the above-cited portion of the '773 patent that photolysis actually induces removal of the NVOC protecting group. Thus, it is apparent that the NVOC protecting group is not functioning as an autocatalytic compound. Accordingly, the combination of the '974 patent (having an issue date of September 7, 1993) and the '773 patent (having an issue date of October 21, 1997, which is after the present effective filing date of November 14, 1996) does not show that the NVOC protecting group necessarily or inherently functions as a catalyst or an autocatalyst.

In view of the foregoing, Applicants have provided independently sufficient bases for the patentability of claims 1, 52, and 70 and all claims dependent therefrom over the '974 patent and the '773 patent. However, to be fully responsive to the present Office Action, the following comments are provided.

Claims 12, 53, and 71 are additionally patentable over the '974 patent and the '773 patent because of similar reasons presented above. The Examiner asserts that the '773 patent at column 18, lines 43-54 teaches a photolabile NVOC protecting group that is cleaved into an acid catalyst (6,6-bisveratric acid) by light. Applicants respectfully disagree because, as discussed in detail above, 6,6-bisveratric acid is not a catalyst. Upon photolysis, the NVOC protecting group is cleaved into 6-nitrosoveratraldehyde as an unstable intermediate which, upon acid catalysis, forms 5,6-dimethoxy-2,1-benzisoxazol-3(1H)-one. As previously mentioned, 6,6-bisveratric acid is not actually synthesized until further photolysis of 5,6-dimethoxy-2,1-benzisoxazol-3(1H)-one. Nowhere does the '773 patent disclose that 6,6-bisveratric acid is functioning as a catalyst. Thus, claims 12, 53, and 71 are patentable for this additionally, independently sufficient reason.

Claims 15, 56, and 73 are additionally patentable over the '974 patent and the '773 patent because, as discussed above, 6,6-bisveratric acid is not acting as a catalyst or an autocatalyst. Again, the Examiner asserts that the NVOC protecting group is cleaved into an acid catalyst (6,6-bisveratric acid) by light. As discussed in detail above, 6,6-bisveratric acid is not acting as a catalyst. Accordingly, claims 15, 56, and 73 are patentable over the cited references for this independently sufficient reason.

With regard to claim 57, the Examiner asserts that the '773 patent teaches an acid labile NVOC protecting group. Applicants traverse this rejection because the cited portion of the '773 patent (column 18, lines 43-54) only teaches that the NVOC protecting group is photoremovable – the NVOC protecting group is not necessarily acid labile. Holmes merely states that photodeprotection is typically conducted in an organic solvent containing an acid such as sulfuric acid. Nowhere does the '773 patent disclose that photodeprotection *must* occur in an acidic environment. Accordingly, claim 57 is patentable over the cited references for this independently sufficient reason.

V. Claims 1-2, 6, 12, 15, 52, 53, 55, 57, 60, 70-72, and 76 Are Patentable Over MacDonald

Claims 1-2, 6, 12, 15, 52, 53, 55, 57, 60, 70-72, and 76 stand rejected under 35 U.S.C. § 102(b) over MacDonald. Applicants respectfully traverse this rejection.

The Examiner asserts on page 11 of the present Office Action that MacDonald discloses trifluoromethane sulfonic acid (acts as a catalyst) which can cleave the t-BOC protecting group and can also cleave more triphenylsulfonium hexafluoroantimonate (acts as an autocatalytic compound), i.e., triphenylsulfonium hexafluoroantimonate functions as both a radiation sensitive compound *and* an autocatalytic compound. Applicants respectfully disagree with the Examiner

because triphenylsulfonium hexafluoroantimonate is not an autocatalyst as defined by the pending claims.

MacDonald fails to disclose an autocatalytic compound or group, as defined by independent claims 1 and 52 and dependent claim 15. At page 11, lines 25-26, Applicants explain, "An autocatalyst is a material that undergoes a reaction that produces a product that is also a catalyst for that same reaction." As seen in FIG. 3 of MacDonald, triphenylsulfonium hexafluoroantimonate is not undergoing a reaction that produces a product that is a catalyst for *that same reaction*. That is, triphenylsulfonium hexafluoroantimonate undergoes a reaction that produces trifluoromethane sulfonic acid, which is a catalyst for the *subsequent reaction* of cleaving the *tert*-butylcarbonate protecting group. It is readily apparent from the disclosure of MacDonald at p. 152, column 2 that photolysis actually induces the production of the trifluoromethane sulfonic acid catalyst:

However, in order to use this acid-catalyzed thermolysis for lithography, one **must be able to photochemically generate acid**. . . Upon heating to 100 °C, **the acid catalyzes the decomposition of the t-BOC groups** with release of CO₂ and isobutylene (Figure 3). . . (Emphasis added).

Nowhere does MacDonald disclose explicitly or inherently that trifluoromethane sulfonic acid catalyzes the production of more trifluoromethane sulfonic acid. Accordingly, MacDonald fails to disclose an autocatalytic compound or group.

In that regard, since MacDonald fails to disclose an autocatalytic compound or group, as described above, it logically follows that MacDonald also fails to disclose an autocatalytic compound or group generating a protecting group removing product when the autocatalytic compound is activated by the catalyst. That is, while triphenylsulfonium hexafluoroantimonate produces trifluoromethane sulfonic acid during photolysis, MacDonald does not disclose (and the Examiner has not shown with support) that triphenylsulfonium hexafluoroantimonate catalyzes

the production of more trifluoromethane sulfonic acid. Accordingly, MacDonald does not disclose an autocatalyst as defined by independent claims 1 and 52 and the specification. As such, MacDonald does not disclose an autocatalyst that generates a protecting group removing product. Thus, claims 1, 52 and all claims dependent therefrom, directly or indirectly, are patentable over MacDonald for at least the foregoing reasons.

Further, independent claim 70 is patentable over MacDonald at least because MacDonald fails to disclose a synthesis intermediate, as defined by claim 70. The Examiner asserts that MacDonald discloses “a poly[4-(terbutoxycarbonyl)poly-carbonate-oxy]styrene, which is a “synthesis intermediate.” Applicants believe the Examiner is referring to “poly[4-[(tert-butyloxycarbonyl)oxy]styrene” (also known as “PBOCST”) disclosed at page 152, column 2 of MacDonald. Specifically, the Examiner asserts at page 19 of the present Office Action that the PBOCST taught by MacDonald is a teaching of a synthetic intermediate because once the t-BOC protecting group is removed, the phenol moiety is available to react with another compound, namely $\text{Me}_2\text{N-SiMe}_3$, as seen in FIG. 11. Applicants respectfully traverse this rejection in view of the following discussion.

MacDonald’s disclosure of PBOCST is not equivalent with a synthesis intermediate as understood from the present disclosure. Applicants teach, for example, at page 4, lines 9-24 of the application, that a synthesis intermediate may, in certain preferred embodiments, be subsequently added to the substrate to react with additional synthesis intermediate:

Stated differently, the radiation initiates a chemical reaction which catalyzes the removal of a large number of protective groups. With the protective groups removed, the reactive functional groups of the linker molecules are made available for reaction **with a subsequently added synthesis intermediate or other compound.**

The substrate is then washed or otherwise contacted with an additional synthesis intermediate that reacts with the exposed functional groups on the linker molecules to form a sequence. In some preferred embodiments, the enhancers are

autocatalytic compounds or groups that undergo autocatalysis when initiated by a RAC such as a PAC. The synthesis intermediate also has a reactive functional group which is blocked or otherwise made unavailable for reaction by a removable protective group. In this manner, a sequence of monomers of any desired length can be created by stepwise irradiating the surface of the substrate to initiate a catalytic reaction to **remove a protective group from a reactive functional group on a already present synthesis intermediate and then introducing a monomer, i.e. a synthesis intermediate, that will react with the reactive functional group**, and that will have a protective group for later removal by a subsequent irradiation of the substrate surface. (Emphasis added).

Thus, as used here, the synthetic intermediate is capable of reacting with (1) additional synthetic intermediate and/or (2) another compound. That is, in certain preferred embodiments, once the protecting group is removed from Applicants' synthesis intermediate, the reactive moiety of the synthesis intermediate is available to react with additional synthesis intermediate and/or another compound.

In contrast, MacDonald does not disclose that PBOCST may be subsequently added to the substrate to react with additional PBOCST or other compound. That is, MacDonald does not disclose (and the Examiner has not demonstrated) how PBOCST (with the t-BOC protecting group removed) is capable of reacting with more PBOCST. Applicants respectfully believe that the Examiner's assertion that PBOCST is a synthetic intermediate misses the mark as MacDonald's teaching of unprotected PBOCST reacting with $\text{Me}_2\text{N-SiMe}_3$ is only a teaching of the unprotected PBOCST reacting with *another compound*, which is only half of the definition of Applicants' "synthesis intermediate". Nowhere does MacDonald disclose (or even suggest how) unprotected PBOCST can react with additional PBOCST. Thus, PBOCST is not a synthetic intermediate as that term is used here. Accordingly, claim 70 and all claims dependent therefrom are patentable over MacDonald for at least this reason.

In addition, dependent claim 6 is patentable over MacDonald, contrary to the Examiner's assertion, because MacDonald does not disclose a synthesis intermediate selected from the group

consisting of a nucleotide, a DMT protected nucleotide, a polynucleotide, an amino acid, and a polypeptide. The Examiner asserts that MacDonald's teaches synthesizing various types of polymers including peptides (see MacDonald, page 152, last paragraph). Applicants respectfully disagree because the only polymer MacDonald teaches at page 152, last paragraph is poly[4-[(tert-butyloxycarbonyl)oxy]styrene, which is not a nucleotide, a DMT protected nucleotide, a polynucleotide, an amino acid, or a polypeptide. Thus, claim 6 is patentable over MacDonald for this additional, independently sufficient reason.

Because MacDonald fails to disclose all of the claim limitations of all pending independent claims, Applicants respectfully request removal of the present rejection at this time.

VI. The Subject Matter Defined by Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 Does Not Constitute New Matter

Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 stand rejected under 35 U.S.C. § 112, ¶1. Specifically, the Examiner asserts that Applicants' previous amendment to independent claims 1, 52, and 70 in which the phrase "synthesis intermediate" in the preamble was previously replaced with the phrase "reactive functional group" constitutes new matter. Applicants traverse this rejection in view of the following remarks.

Independent claims 1, 52, and 70 as previously amended defined a method for removing a protecting group from a reactive functional group. Applicants note that support for the previous amendment is found throughout the specification, for example, at page 3, lines 20-22, "The unbound portion of the linker molecule, also referred to as the terminal or free end of the linker molecule, has **a reactive functional group** which is blocked, protected or otherwise made unavailable for reaction by a **removable protective group**." (Emphasis added). Support for the amendment is also found at page 4, lines 17-18, "The synthesis intermediate also has **a reactive**

functional group which is **blocked** or otherwise made unavailable for reaction **by a removable protective group.**" (Emphasis added). Thus, the subject matter defined by independent claims 1, 52, and 70 as previously amended did not constitute new matter. Accordingly, Applicants traverse the Examiner's rejection.

Nevertheless, Applicants have amended claims 1, 52, and 70 to define a method for removing a protecting group from a linker molecule or a synthesis intermediate. Support for the amendment can be found throughout the specification, for example, at page 4, lines, 17-18: "The **synthesis intermediate also has** a reactive functional group which is blocked or otherwise made unavailable for reaction **by a removable protective group.**" (Emphasis added). Additional support can be found at page 3, lines 18-22:

According to one embodiment of the present invention, one or more linker molecules are bound to or otherwise provided on the surface of a substrate, such as a glass plate. The unbound portion of the **linker molecule, also** referred to as the terminal or free end of the linker molecule, **has** a reactive functional group which is blocked, protected or otherwise made unavailable for reaction **by a removable protective group.** (Emphasis added).

Thus, as the language "reactive functional group" is no longer recited in claims 1, 52, and 70, Applicants respectfully request removal of the present rejection at this time.

VII. Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 Satisfy the Written Description Requirement

Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 stand rejected under 35 U.S.C. § 112, ¶1 pursuant to the written description requirement. Applicants traverse this rejection in view of the following remarks.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1 "Written Description" Requirement specifies that a patent specification must describe the

claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. 66 Fed. Reg. 1,104 (2001). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formula that fully set forth the claimed invention. *Id.*

The Examiner asserts that the phrase “reactive functional groups” recited in the claims 1, 52, and 70 as previously amended is defined only by its function. As mentioned above, claims 1, 52, and 70 as currently amended now define a method for removing a protecting group from a linker molecule or a synthesis intermediate instead of “reactive functional groups.” As mentioned above, the methods defined by claims 1, 52, and 70 as amended are described throughout the specification, e.g., at page 3, lines 18-22 (quoted above). As such, claims 1, 52, and 70 define subject matter such that that one skilled in the art can reasonably conclude that Applicants had possession of the claimed inventions. Accordingly, Applicants’ description of the presently claimed methods in the specification meets the § 112, ¶1 written description requirement and removal of the present rejection is respectfully requested at this time.

VIII. Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 Satisfy the Definiteness Requirement

Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 stand rejected under 35 U.S.C. § 112, ¶2. Applicants traverse this rejection in view of the following remarks.

The Examiner asserts that the phrase “making the reactive functional group available for reaction with a synthesis intermediate or other compound” is vague and indefinite. Claims 1, 52, and 70 as presented above no longer recite the phrase “making the reactive functional group available for reaction with a synthesis intermediate or other compound”. Accordingly, Applicants deem the present rejection overcome.

The Examiner further asserts that the phrase "reactive functional group" is vague and indefinite. As discussed above, claims 1, 52, and 70 no longer recite the phrase "reactive functional group." Instead, each of claims 1, 52, and 70 now define a method for removing a protecting group from a linker molecule or a synthesis intermediate. Accordingly, a person of ordinary skill in the art can readily determine the metes and bounds of claims 1, 52, and 70 as currently presented given the benefit of the present disclosure. Thus, Applicants respectfully request removal of the present rejection at this time.

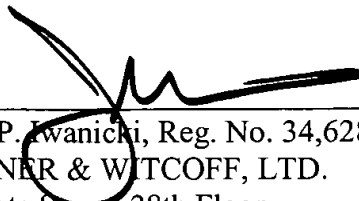
IX. Conclusion

Applicants have shown that the '773 patent, the '974 patent, and MacDonald each do not anticipate the pending claims. Further, Applicants have clearly demonstrated that the specification as filed meets the requirements of § 112, ¶1 and the definiteness requirement of § 112, ¶2.

Having addressed all outstanding issues, Applicants respectfully request allowance of the case at this time. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

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